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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,937	MATA LOPEZ ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-12 and 15-26* is/are pending in the application.

4a) Of the above claim(s) *1-6,9-12,18 and 21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply; CRFD*.

DETAILED ACTION

Claims 1-6, 9-12, and 15-26 are pending.

Claims 1-6, 9-12, 18, and 21-26 are withdrawn from examination as detailed below.

Claims 15-17, 19, and 20 are examined on the merits.

Election/Restrictions

1. Applicant's election of the invention of Group 3 (methods of diagnosis comprising mutation detection) and the particular mutation of 313+1insT and the oligonucleotides of SEQ ID NO: 56-59 (related to detection of 313+1insT) in the reply filed on 09/29/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-6, 9-12, 18, and 21-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (i.e. non-elected products (claims 1-3, 5, 6, 9, 10, 12, 18) and methods (claim 4), and methods specifically requiring non-elected combinations of SEQ ID NOs and mutations (claims 11, 21-26) there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 09/29/2008.

Improper Multiple Dependent Claim Objection

2. Claim 16 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only, where

claim 16 recites 'according to claims 13 to 15'. See MPEP § 608.01(n). Accordingly, the claim 16 has not been further treated on the merits.

Sequence Compliance

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 at least for the reason(s) set forth below:

> The computer readable form (CRF) of the sequence listing that was submitted 09/29/2008 was found to be defective, as such the application fails to comply with the Sequence Rules set forth in 1.821. Please see the Notice to Comply and Sequence Listing Error Report (CRFD).

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), the specification must included an error-free CRF of the sequence listing.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example pages 3 and 4 of the specification; applicant should inspect the specification in its entirety to ensure that all browser-executable code is removed. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

5. Claim 19 is objected to because of the following informalities:

Claim 19 recited the term 'familiar' where the term 'familial' is likely intended.

Appropriate correction is required.

Claims 15 and 17 are objected to for the specific recitation of non-elected subject matter in the alternative. In the response of 09/29/2008 Applicants have elected for the examination of the invention as it requires the 313+1insT mutation and the related oligonucleotides of SEQ ID NO: 56-59. Claim 15 encompasses any combination of at least one of approximately 54 different specifically recited mutations. Similarly, claim 17 encompasses any combination of the many different specifically recited oligonucleotide sequences. It is noted that no claim has been found allowable in this Office Action. Prior to the allowance of any claim, any non-elected subject matter that has not been rejoined with the examined subject matter will be required to be removed from the claims.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 15, 17, 19, and 20 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The rejected claims are drawn to methods for diagnosis of familial hypercholesterolemia. The claimed invention falls within an enumerated statutory category, namely a process.

The rejected claims are drawn to methods for diagnosis comprising the single step of detecting in a biological sample of an individual the 313+1insT mutation.

In re Bilski No. 2007-1130 (Fed Cir. October 30, 2008) characterizes its machine-transformation test as "the governing test for determining patent eligibility of a process under section 101." Under this test, a process claim is patent-eligible if (and, as applied in Bilski, only if): "(1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." The claims are not directed to patent-eligible subject matter since they are not tied to any particular machine or apparatus and they do not require any particular article to be transformed into another state or thing.

None of the rejected claims requires the transformation of an article or physical object to a different state. For example, relevant to the rejected claims, one could detect the mutation merely by consulting a digital record in an electronic database of nucleic acid sequence information previously derived during a genome sequencing project. Additionally, there is no result tied to the physical world. There is no required transformation of an article or physical object to a different state. Transformation of data is not considered a physical transformation.

As clearly noted in In re Comiskey No. 2006-1286 (Fed. Cir. Sept. 20, 2007), "the Supreme Court has reviewed process patents reciting algorithms or abstract concepts

in claims directed to industrial processes. In that context, the Supreme Court has held that a claim reciting an algorithm or abstract idea can state statutory subject matter only if, as employed in the process, it is embodied in, operates on, transforms, or otherwise involves another class of statutory subject matter, i.e., a machine, manufacture, or composition of matter. 35 U.S.C. § 101." Regarding In re Comiskey, the USPTO noted, "[t]he Supreme Court has recognized only two instances in which such a method may qualify as a section 101 process: when the process 'either [1] was tied to a particular apparatus or [2] operated to change materials to a 'different state or thing.'" (quoting Flook, 2006-1286 17 437 U.S. at 588 n.9). In Diehr, the Supreme Court confirmed that a process claim reciting an algorithm could state statutory subject matter if it: (1) is tied to a machine or (2) creates or involves a composition of matter or manufacture. 450 U.S. at 184. There, in the context of a process claim for curing rubber that recited an algorithm, the Court concluded that "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." Id. (quoting Benson, 409 U.S. at 70);13 see also In re Schrader, 22 F.3d 290, 295 (Fed. Cir. 1994) (holding when a claim does not invoke a machine, "§ 101 requires some kind of transformation or reduction of subject matter").

Finally, the Comisky opinion states that mental processes- or processes of human thinking- standing alone are not patentable even if they have practical application. The Supreme Court has stated that "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." Benson, 409 U.S. at 67. In

Flook the patentee argued that his claims did not seek to patent an abstract idea (an algorithm) because they were limited to a practical application of that idea-updating "alarm limits" for catalytic chemical conversion of hydrocarbons. 437 U.S. at 586, 589-90. The Court rejected the notion that mere recitation of a practical application of an abstract idea makes it patentable, concluding that "[a] competent draftsman could attach some form of post-solution activity to almost any mathematical formula." Id. at 590.

In the case of the instant claims, there is no recitation of producing a real-word result that is tied to a machine or apparatus or causes a transformation of an article. In other words, the outcomes of the rejected methods lack a tie to the machine or apparatus and lack a physical transformation. Thus the claims are rejected as encompassing non-statutory subject matter.

The claims may be drawn to statutory subject matter if the methods are amended to specifically require the steps of (a) obtaining a biological sample from a subject, said sample comprising nucleic acids of the subject; and (b) detecting in said nucleic acids the presence of the 313+1insT mutation.

Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 15, 17, 19, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15, 17, 19, and 20 are unclear over recitation of the term '313+1insT', where the specification nor the prior art provide any limiting definition of what nucleotide content in any particular sequence context is required for identification of the required mutation. The claims may be made more clear if amended to require a particular sequence from the specification as originally filed that is indicative of the required mutation, for example 'wherein the 313+1insT mutation is detected by detecting the presence of SEQ ID NO: 58 in the junction of exon 3 and intron 3 in the low density lipoprotein receptor (LDL-r) gene'.

Claims 15, 17, 19, and 20 are unclear over the stated purpose of the claimed methods as 'of *in vitro* diagnosis of familial hypercholesterolemia' as recited in the preamble of independent claims 15 and 19. The rejected methods comprise only the single method step of detecting in a sample the 313+1insT mutation. However the single step of detecting a mutation does not render a diagnosis. The claims may be made more clear if amended to require a step of correlating detected nucleotide content with a diagnosis of familial hypercholesterolemia, or if amended to recite a clause specifying wherein the presence of particular detected nucleotide content is indicative of a diagnosis of familial hypercholesterolemia.

Claim 20 is unclear over the limitation that the claimed oligonucleotides 'are capable of hybridizing to the mutation 313+1insT'. The claim recites four different

oligonucleotides which appear to comprise the sequence of different forms of the 313+1insT mutation, but the claim requires that all of the recited oligonucleotides are capable of hybridizing to the mutation. It is therefor unclear as to what nucleotide content Applicants intend to be required for 'the mutation 313+1insT'.

Claim Rejections - 35 USC § 112 1st¶ - Written Description

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 15, 17, 19, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants are directed to the Written Description Training Materials revised March 25, 2008, available online at www.uspto.gov/web/menu/written.pdf.

The rejection of claims for lack of adequate written description is relevant the requirement of the claims, as consonant with the Election, of 'the mutation of 313+1insT' (as recited in the claims, consonant with the Election) with the required functionality of being diagnostic of familial hypercholesterolemia. In the instant case the specification

does not provide the skilled artisan with an adequate written description of a particular mutation, with the required diagnostic functionality, identified by the term '313+1insT'.

The specification provides no limiting definition as to what nucleotide content in a particular sequence context is required to be indicative of the '313+1insT' mutation. Thus when the claims are analyzed in light of the specification, the claims encompass a large genus of nucleotide contents in a variety of sequence contexts: position '313' may be a relative position starting from a transcription start site, some arbitrary genomic location, a translation start site. The lack of nucleotide sequence context in view of the recitation of a mutation with a functional requirement in a diagnostic method is particularly relevant in view of the prior art references which teaches the difficult in assigning any familial hypercholesterolemia (FH)-related functionality to mutation in the LDL receptor. For example, Lombardi et al (1997) indicates that a particular mutation previous accepted as causative of FH was not associated with FH in another different study.

Relevant to the lack of particular structural limitations in the rejected claims, MPEP 2163 states:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art.

In the instant claims, the detection of particular nucleotide content at a particular position, and the correlative association of that content with FH is critical to the claimed invention. However, given the particular recitations in the claims and the lack of limiting structural requirements of the required mutation in the specification, one of skill in the

art can not a priori identify the required mutation required of the claims which have the particular diagnostic functionality.

In conclusion, having considered the breadth of the claims, and the particular teachings of the instant specification, and the teachings of the prior art, the specification, while providing a written description of methods requiring detection of:

> The 313+1insT mutation, wherein the 313+1insT mutation is detected by detecting the presence of SEQ ID NO: 58 in the junction of exon 3 and intron 3 in the low density lipoprotein receptor (LDL-r) gene'

does not provide an adequate written description of the broadly claimed subject matter.

Claim Rejections - 35 USC § 112 1st ¶ - Enablement

10. Claims 15, 17, 19, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The instant claims are drawn to methods of in vitro diagnosis of familial hypercholesterolemia (FH) comprising detecting the mutation 313+1insT (as consonant with the Election).

The claims broadly encompass the detection of any nucleotide content that is 'the 313+1insT mutation' as recited in the claims but not structurally defined by either the claims or the instant specification.

The claims encompass the analysis of any subject organism.

The claims these require knowledge of a diagnostic association between the broadly claimed nucleotide content of 'the 313+1insT mutation' and the presence of FH.

Direction provided by the specification and working example

The specification provides an example of the identification of new mutant variants in the low density lipoproteins receptor (LDL-R) gene. The specification teaches (p.23-24), relevant to the Election, the identification of the 313+1insT mutation. The specification provides that the mutation was detected in a single particular human subject that was clinically diagnosed as having FH. The specification teaches that the 313+1insT mutation may be detected with SEQ ID NO: 56-59, where relevant to the sequence set forth in SEQ ID NO: 1 of the paper sequence listing, the aforementioned SEQ ID NO: 56-59 detect the insertion of a T between positions 28562 and 28563.

The specification does not teach the analysis of the 313+1insT mutation in any other subjects. There is no case:control analysis of the mutation, and there is no family-based study to analyze cosegregation of the mutation.

There is no analysis of any mutation or phenotype in any non-human subjects.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art with regard to the detection of any particular nucleotide sequence is high, the unpredictability with regard to the association of any particular sequence with a particular phenotype, or the identification of any nucleotide sequence has having a particular functionality, is even higher. The unpredictability is demonstrated by the prior art and the post-filing art.

The claims of the instant application encompass any mutation that is a '313+1insT' mutation. The lack of structural requirements (i.e. there is no limiting definition in the specification as to the sequence content or context required for the mutation) of the recited mutation, as consonant with the Election, has been discussed earlier in this Office Action. Because the diagnostic methods of the claims are not limited to any particular nucleotide sequence content, it is relevant to point out the unpredictability in associating any sequence content with a particular phenotype. For example, Hacker et al (1997) teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627).

Because the claims encompass diagnostic methods in any subject organism, it is relevant to point out the unpredictability in extrapolating the presence of polymorphic nucleotide content, or its association with any phenotype, form one animal to any other different animal. Such unpredictability in interspecies extrapolation is addressed by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S).

And while the claims are generically drawn to diagnostic methods comprising detecting the 313+1insT mutation, while the instant specification teaches only the detection of the recited mutation in a single particular subject, it is relevant to point out the unpredictable nature of any mutation association study. As evidence of the

unpredictability of gene association studies, Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph). Additionally, Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

The unpredictability as generally described by Lucentini and by Hegele, as cited above, is particularly relevant considering the teachings of the prior art. For example, while many mutations have been previously identified in the LDL-R gene of FH patients, the identification of a sequence deviation in a subject is not sufficient to indicate that the mutation is reliably diagnostic of the phenotype. Lombardi et al (2007) teaches a follow-up analysis of a particular mutation that was previously considered causative of FH. In

the follow-up study there is a lack of cosegregation of the mutation with the FH phenotype (p.107, left col.; Fig 1).

Finally, while the claims encompass diagnostic methods while the specification teaches the identification of a mutation in only a single affected individual, it is relevant to point out that the prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant (Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion).

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the claimed invention. Such experimentation would include large case:control studies in populations of any subject organism to demonstrate a robust and reliable association of different nucleotides contents with FH. Even for the particular 313+1insT mutation disclosed in the specification, one would have to perform large case:control studies to establish whether or not the asserted associations are reliable and robust. Such experimentation would be extensive. Even if one were to carry out such experimentation, there is no assurance that a reliable and consistent association of genetic content consonant with the Elected invention with FH would be identified.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Art Unit 1634